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Effect of vitamin D on prognosis in patients with gastric cancer

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ABSTRACT

Aims: In the Eastern Anatolia Region of Turkiye it is estimated that the gastric cancer is seen more frequently compared to other regions. As is well known, a reduction in the incidence of certain cancers with high vitamin D value was identified, and vitamin D has been shown to have positive effects on the prognosis of these diseases. In our study, we aimed to investigate the relationship between vitamin D values before treatment and prognosis in patients with gastric cancer.

Methods: This study includes 76 patients who had diagnosis of gastric cancer for the first time and admitted to Oncology Clinic in Van Yüzüncü Yıl University (YYU) Faculty of Medicine Hospital. Patients inclusion criterias have been identified as lack of story for recently blood transfusion, treatment with any medication and being taken any mineral supplements. Patients vitamin D and tumor markers values were measured at diagnosis. Vitamin D values at diagnosis and stage of the disease, 6. 12. month mortality and disease progression were compared.

Results: A total of 76 patients were included in the study. Mean value of vitamin D was 16.1 (3-27). There was not a significant correlation between vitamin D value and stage of disease. Mean age was 60 (33-89). Of the patients 26 (34.2 percent) had no metastasis, 15 (19.2 percent) had only liver metastasis, 8 (10.5 percent) had only lung metastasis and 27 (35.5 percent) had two or more region metastasis.

Conclusion: In our study, vitamin D deficiency was present in all gastric cancer patients regardless of stage, indicating that vitamin D deficiency is a poor risk factor in gastric cancer.

Keywords: Gastric cancer, vitamin D value, prognosis

INTRODUCTION

Gastric cancer is one of the leading causes of cancer-related deaths worldwide, with a mortality rate of 9.4%.[1] Although the incidence and mortality of gastric cancer have decreased in recent years, it remains one of the top four causes of cancer-related deaths globally.[1,2] The reduction in mortality can be attributed to early detection of the disease.[3] The availability of laboratory tests and the widespread use of appropriate replacement therapies in cancer patients are estimated to decrease mortality. Gastric cancer is the fourth most common cancer worldwide. Early detection and control of risk factors are the most effective methods of prevention, given its low 5-year survival rate. According to data from the World Health Organization (WHO), the most common types of cancer worldwide are lung cancer (12.3%), breast cancer (10.4%), and colorectal cancer (9.4%). The leading causes of cancer-related deaths are lung cancer (17.8%), gastric cancer (10.4%), and liver cancer (8.8%).[5] Epidemiological studies indicate that smoking, Helicobacter pylori infection, and diet are significant risk factors for gastric cancer. Gastric cancer is believed to result from a complex interplay between environmental and genetic factors.[4]

Although vitamin D is primarily associated with calcium and bone metabolism, it has been shown to have various biological functions, including an anticancer effect. The first study in this area was Apprely's observation of the correlation between cancer mortality and solar radiation in North America.[6]

Intensive research on this subject began 35 years ago when Garland demonstrated the North-South relationship with cancer rates. High cancer incidences were found in the north and low in the south.[7] Gıovanunnuci's study supports the hypothesis that vitamin D is cancer-protective. These studies found that deaths from colon, prostate, and breast cancers were 30% lower in summer months compared to winter months. According to these studies, it is recommended that patients receive a daily replacement of 1000 IU of vitamin D, particularly during the winter months.[8]

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It is estimated that gastric cancer is more prevalent in Eastern Anatolia than in other regions of Turkiye. High levels of vitamin D have been shown to reduce the incidence of certain cancers and have a positive impact on disease prognosis.[8] Studies have proven that high levels of vitamin D have a protective effect against prostate, breast, and colorectal cancers.[2-8] In this study, we aimed to investigate the relationship between pre-treatment vitamin D levels and the prognosis of patients diagnosed with gastric cancer.

METHODS

This study included 76 patients who were admitted to the Oncology outpatient clinic of Van Yüzüncü Yıl University (YYU) Faculty of Medicine Hospital and were diagnosed with gastric malignant neoplasm for the first time. The study population consisted of both genders and individuals over the age of 18. Patients were enrolled prior to the initiation of any treatment. The inclusion criteria for the patients were as follows: no recent history of blood transfusion and no current use of medication or mineral supplements for therapeutic purposes. All patients were questioned about their history of chronic liver and kidney disease, and a complete physical examination was performed.

Tumor markers and vitamin D levels were measured at the time of diagnosis. The study compared vitamin D levels at diagnosis with disease stage, 6- and 12-month mortality, and disease progression [radiologically or by positron emission tomography (PET)].

Venous blood samples (2-3 milliliters) were collected from each participant. Samples showing hemolysis were excluded. The blood was allowed to clot and then centrifuged at 3000 rpm for 15 minutes to separate the serum. The serum samples were stored in deionized polyethylene tubes and in a deep freezer at -80 degrees Celsius until the day of the study.

Biochemical analysis was conducted on blood samples obtained from the patients to determine CEA, CA 19-9, and vitamin D levels. The samples were analyzed using the chemiluminescence method on Arcitech CİI16200 (Abbott Agnostos IL USA).

The study received ethics committee approval from Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 05.05.2015, Decision No: 2015/13). The analyses were conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Descriptive statistics were used to express the emphasized characteristics as mean and standard deviation (Mean±SD). The groups were compared in terms of these characteristics using One-way analysis of variance (One-way ANOVA). A statistical significance level of 5% was used for calculations. The statistical package program SPSS for Windows version 13.0 was used.

RESULTS

A total of 76 patients who were diagnosed with gastric cancer and followed up and treated in the Department of Medical Oncology, Yüzüncü Yıl University Faculty of Medicine were included in the study. Of these, 47 (61.8%) were male and 29 (37.2%) were female. The male to female ratio was 1.62/1.

In the male group, 3 patients had stage 2, 11 patients had stage 3, 33 patients had stage 4 disease; in the female group, 4 patients had stage 2, 8 patients had stage 3, 17 patients had stage 4 disease. In total, 7 patients had stage 2, 19 patients had stage 3, and 50 patients had stage 4 disease.

The mean vitamin D level was 16.1 (3-27), 15.7 (13-18) in stage 2 patients, 16.9 (7-27) in stage 3, 15.9 (3-26) in stage 4 and no significant correlation was found between the stage of the disease and vitamin D level (**Table 1**).

Table 1. Vitamin D levels according to stages and comparison of vitamin D values according to stages

	Number	Mean	Std. Dev.	Std. err	Min.	Max.
Stage 2	7	15.7286	2.37397	.89727	13.20	18.90
Stage 3	19	16.9105	5.31318	1.21893	7.20	27.90
Stage 4	50	15.9660	4.52479	.63990	3.60	26.90
Total	76	16.1803	4.55927	.52298	3.60	27.90
	(I) Stage	(J) Stage		Std. err	P	
Tukey HSD						
	Stage 2	Stage 3		2.03417	.831	
		Stage 4		1.85665	.991	
	Stage 3	Stage 2		2.03417	.831	
		Stage 4		1.23991	.727	
	Stage 4	Stage 2		1.85665	.991	
		Stage 3		1.23991	.727	

The patients' mean age was 60 (33-89), with stage 2 patients having a mean age of 65 (46-89), stage 3 patients having a mean age of 60 (40-74), and stage 4 patients having a mean age of 60 (33-84). The mean CEA level for tumor markers was 57 (1-1000), and the mean CA 19-9 level was 189 (2-1200).

Metastases were absent in 26 patients (34.2%). The liver was the most common site of visceral metastasis. **Table 2** displays the frequency of metastases.

Table 2. Metastatic regions

	Frequency	Percentage
Null	26	34.2
Liver	15	19.7
Lung	8	10.5
2 and more regions	27	35.5
Total	76	100.0

Out of the patients, 28 (36.8%) received MDCF (modified docetaxel-cisplatin-5 fluorouracil), 10 (13.2%) received CF (cisplatin-5 fluorouracil), 11 (14.5%) received capecitabine, 16 (21.1%) received other treatments, and 11 (14.5%) received more than one treatment.

According to data from the World Health Organization, patients were divided into two groups based on their vitamin D levels: those with levels below 20 ng/ml[9] and those with levels above 20 ng/ml. At the 6-month tumor response evaluation, 34 patients progressed. All of these patients had vitamin D levels below 20 ng/ml. In contrast, no progression was detected in patients with vitamin D levels above 20 ng/ml at 6 months. There was a significant difference between these two groups (p:0.01) (**Table 3**).

Table 3. Progression according to 6. Month vitamin d levels

	Vitamin D		Total	Q-square
	<20	>20		P value
Progression at 6.month				0.01
No	30	12	42	
Yes	34	0	34	
Total	64	12	76	

At 12 months, progression was detected in 50 patients, 43 of whom had vitamin D levels below 20. The remaining 7 patients had vitamin D levels above 20. At 12 months, there was no significant difference in progression rates between the two groups (p=0.314). Please refer to **Table 4** for more information.

Table 4. Progression by 12th month vitamin d levels

	Vitamin D		Total	q-square
	<20	>20		P value
Progression at 12. month				0.314
None	16	5	21	
Yes	43	7	50	
Total	59	12	71	

DISCUSSION

Although the incidence and mortality rates of gastric cancer have decreased worldwide in recent years, it remains the 4th most common cancer and the 3rd most common cause of cancer-related deaths.[10] According to the Surveillance, Epidemiology and End Results (SEER) database, it accounts for 1.6% of new cancer cases in the United States.

In Turkiye, the situation is different, and stomach cancer ranks 5th in men and 6th in women in terms of incidence (Globocan 2013 data). Memik et al.[11] found significant differences in gastric cancer incidence between the eastern and western regions of the country. Gastric cancer accounted for 9.4% of all cancers. In a 2003 study of 1002 cases in the Van Lake basin, Tuncer et al.[12] reported that gastric cancer was the most common gastrointestinal malignancy, comprising 47% of cases. The study reported a male/female ratio of 2/1 and mean ages of 55 for women and 58 for men.

Vitamins are essential for the body and refer to substances that cannot be produced internally and must be obtained through food. Vitamin D, one of the most important vitamins, is also a hormone, unlike other vitamins. Approximately 80-90% of this steroid hormone is synthesized endogenously in the skin, while the remaining 10-20% is obtained exogenously from plant and animal sources through diet. The circulating serum concentrations of 1,25(OH)2D3 are approximately 0.1% of 25OHD3. Vitamin D synthesis is primarily regulated by the key enzyme 1α-hydroxylase, which is in turn regulated by parathormone, calcium, 1,25(OH)2D3, and fibroblast growth factor-23 (FGF-23). The activation of 1,25(OH)2D3 occurs through binding to vitamin D receptors. This receptor belongs to the steroid receptor family and is found in both the cytoplasm and nucleus. This receptor belongs to the steroid receptor family and is found in both the cytoplasm and nucleus. It regulates the expression of approximately 500 genes.

Vitamin D, which mainly regulates Ca and P metabolism, binds to nuclear receptors and increases intestinal Ca and P absorption by increasing the synthesis of proteins required for absorption. It also increases the reabsorption of Ca and P from the kidney. Stimulating osteoblasts in bone, increases Ca release, thus promoting bone mineralization and balancing the storage and release of Ca and P in bone. Vitamin D plays a major role in maintaining appropriate plasma Ca levels.

Vitamin D deficiency has been associated with various disorders, including diabetes, hypertension, cardiovascular diseases, infections, autoimmunity, asthma, obesity, skin diseases, muscle diseases, and cancer. It is estimated that 15-20% of the global population has a vitamin D deficiency. Studies in our country have also shown high rates of vitamin D deficiency, reaching up to 80% in women of reproductive age. The primary cause of vitamin D deficiency is insufficient exposure to sunlight. Low dietary intake, increased loss of vitamin D (such as in nephrotic syndrome), impaired vitamin D activation, and various drugs are causes of vitamin D deficiency.

The relationship between vitamin D and cancer was first established observationally by Frank L. Apeerly in 1940. People living in the north of the United States were found to have a 2 times higher risk of death due to cancer than those living in the south.

The incidence and survival of renal cell cancer were found to be affected by low vitamin D levels in the European Prospective Investigation into Cancer and Nutrition (EPIC) study conducted by Muller et al.[13] among renal cell cancer patients.

A review by Barreto et al.[14] explored the potential of vitamin D and its analogs in preventing and treating pancreatic cancer. The study found that pancreatic cancer tissue expresses vitamin D receptors and that vitamin D may have an impact on pancreatic cancer.

Another study published in the same year by Abulkhair et al.[15] observed that low levels of vitamin D at baseline in breast cancer patients increased the risk of triple negative breast cancer with poor prognosis.

A study conducted on American men found that the incidence and mortality of gastrointestinal cancer was higher in the black race compared to the white race. The study also found that low vitamin D levels were associated with high cancer incidence and mortality in the black race.[16]

In the early 1980s, Colston et al.[17] demonstrated that the doubling time of malignant melanoma cells was extended after incubation with active vitamin D. During the same period, Abe et al.[18] found that leukemia cells differentiated towards the macrophage series after incubation with vitamin D.

Vitamin D is believed to have anti-neoplastic properties through inhibiting proliferation, inducing differentiation and programmed cell death, as well as inhibiting angiogenesis and invasiveness.[19]

In a separate study, SCC cells were photographed two days after treatment with either ethanol or vitamin D. Flow cytometric analysis was then performed. The cells treated with vitamin D were found to be flattened, and there was a significant increase in the number of cells undergoing apoptosis with flow.[20]

The study found that vitamin D deficiency was an independent factor in cancer mortality but not a risk factor in cancer development.[21]

A study conducted in elderly women investigated the relationship between vitamin D and cancer-specific mortality. Another UK-based study investigated the relationship between vitamin D replacement and cancer incidence. In this randomised, placebo-controlled study, 2686 men and women over 65 years of age received vitamin D3 replacement at a dose of 100,000 IU every 4 months. The study found no significant difference in cancer incidence during the 5-year follow-up compared to the placebo group.[22]

The relationship between vitamin D and gastric cancer has been studied less than other types of cancer. Khayatzadeh et al.[23] found no significant relationship between vitamin D and gastric cancer risk. However, Ren et al.[24] discovered that

vitamin D deficiency was a poor prognostic factor in patients with gastric cancer. Patients with serum vitamin D levels of 50 nmol/L and above had significantly longer overall survival. In their 2012 publication, Sungmin Beak et al.[25] demonstrated that vitamin D treatment inhibits gastric cancer cells.

Abnet et al.[26] conducted a study on the relationship between vitamin D and upper gastrointestinal system tumours. The study found no significant correlation between serum vitamin D levels and the risk of upper gastrointestinal system cancer.

Most studies on the topic suggest a weak correlation between serum vitamin D levels and cancer incidence. However, most of the studies on the correlation between serum vitamin D levels and cancer incidence were conducted in regions with intense vitamin D deficiency, and they were mostly epidemiological or experimental. Therefore, it is unclear whether there is a negative correlation between serum vitamin D levels and cancer incidence in areas with normal serum vitamin D levels.

The role of vitamin D in the etiopathogenesis and prognosis of gastric cancer remains unclear. No significant evidence suggests a relationship between vitamin D levels and gastric cancer risk. This study analyses the vitamin D levels at the time of diagnosis and their relationship with overall survival in patients diagnosed with gastric cancer.

Despite being one of the sunniest regions of Turkiye, vitamin D deficiency is observed more frequently than expected in Van province and its surroundings. All patients diagnosed with gastric cancer in our study had low levels of vitamin D. This suggests that vitamin D may be involved in the development of the disease.

In our study, we compared patients with vitamin D levels below 20 ng/ml and above 20 ng/ml. When the progressions of these patients at 6 and 12 months were evaluated, a statistically significant difference in progression-free survival at 6 months and a numerical difference at 12 months was found in the group with vitamin D levels below 20 ng/ml.

The American Institute of Medicine's 2011 report highlighted the beneficial impact of vitamin D on skeletal health. However, the report also noted that there is insufficient evidence to support the use of vitamin D for cancer chemoprevention and treatment.

While vitamin D deficiency is a known cause of colorectal cancer, vitamin D treatment has been found to play a role in colon cancer. Additionally, vitamin D deficiency is an independent risk factor for prostate cancer. Low levels of vitamin D may contribute to the high incidence of gastric cancer in the Van-Erzerum region compared to other regions. Our study found that patients with all stages of gastric cancer had low levels of vitamin D.

Limitations

The study had limitations, including being single-centre, retrospective, and having a small number of patients. Additionally, hormonal disorders that affect calcium metabolism and conditions such as renal insufficiency were not analyzed, which were other limitations of this study.

CONCLUSION

Our study found that vitamin D deficiency is an independent risk factor for many cancers, particularly colon and prostate cancer. Low vitamin D levels were observed in all cases, and patients with lower vitamin D levels at the 6th and 12th months had worse PFS. Low vitamin D levels were observed in all cases, and patients with lower vitamin D levels at the 6th and 12th months had worse PFS. It is important to note that these findings are objective and not influenced by subjective evaluations. Based on this data, it is suggested that a low level of vitamin D may increase the incidence of gastric cancer and act as a poor prognostic factor. However, further support is required through multicentre, prospective studies with larger patient cohorts.

ETHICAL DECLARATIONS

Ethics Committee Approval

The ethics committee approval of the study was obtained from Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 05.05.2015, Decision No: 2015/13).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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